REMARKS

Pending Claims

Claims 1-5 and 11-13 are pending in this application. Applicants request entry of this Amendment and reconsideration of the claims.

Formal Drawings

Formal drawings are submitted with this reply.

Objection to the Specification

The specification has been amended such that the indicated web addresses are no longer operable hyperlinks or operable browser executable code. Withdrawal of this objection is respectfully requested.

35 U.S.C. 112, Second Paragraph

Claims 1-5 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as indefinite. The Examiner suggests the term "TCCR" is arbitrary and fails to distinctly describe the subject matter of the claims. Applicants respectfully traverse.

The term "TCCR" is specifically defined in the patent specification. See, for example, the definition provided at page 14, line 31 through page 17, line 10. This definition includes native TCCR, variants, and TCCR obtained from different species, such as human (SEQ ID NO:1) and murine (SEQ ID NO:2). Applicants also describe some of the characteristics of the receptor at page 86, lines 1-33. Thus, Applicants have described TCCR both structurally and functionally so that one of skill in the art would understand what is meant by the term.

In addition, entry of the term "TCCR" into the NCBI protein data base results in a listing not only of the sequences recited in the specification, but of those previously termed "WSX-1." See attached list. Applicants assert one of skill in the art can readily and specifically determine the protein "TCCR" given the guidance in the specification as discussed above and the information known and available to those in the field.

Withdrawal of this rejection is respectfully requested.

35 U.S.C. 112, Written Description

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description. In particular, the Examiner asserts the specification does not describe or otherwise reduce to practice a TCCR antagonist. In addition, the Examiner asserts the term "TCCR" is indefinite and thus the structure of a "TCCR" which is antagonized is also not described. Applicants respectfully traverse this rejection.

As discussed in MPEP 2163.02, the standard for determining whether an application complies with the written description requirements of § 112, first paragraph, is whether the description clearly allows persons of ordinary skill in the art to recognize that the inventor was in possession of the claimed subject matter as of the filing date. Further, "a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption." MPEP 2163.04. A number of factors can be utilized to establish written description including:

a) full or partial structure;

b) physical and/or chemical properties;

c) functional characteristics;

d) known or disclosed correlation between structure and function;

e) methods of making; and

f) combinations of A-E.

Contrary to the Examiner's rejection, Applicants have provided a description of the structure and function of TCCR. Representative structures of TCCR are described in Figures 3, 4, 5, and at least at page 32, line 20 to page 33, line 6, and at page 86 in the specification. In addition, various domains of the TCCR polypeptides have been identified at pages 7 and page 86, including the WS(G)XWS domain that characterizes cytokine receptors.

Functions of TCCR have been determined using a "knock out" mouse model that is deficient in the gene encoding TCCR, as well as *in vitro* T cell differentiation assays. In Example 12, the role of TCCR in immune response was examined in a knockout mouse model. TCCR deficient cells demonstrated decreased IFN production in response to antigenic

stimulation (Figure 16A). TCCR deficient mice exhibited severely reduced titers of ovalbumin specific IgG2a antibodies. (Figure 17B) When TCCR deficient mice were challenged with *L. monocytogenes*, their ability to mount an immune response to the bacteria was impaired. (Figure 17C). These results demonstrate that TCCR deficient mice are impaired in their ability to mount a Th_1 response, that is, the loss of TCCR resulted in a loss of Th_1 mediated activities.

The claimed invention includes use of TCCR antagonists to reduce Th_1 mediated activities and effect differentiation of T cells to a Th_2 subtype. Antagonists are defined, for example, in the specification at page 26, line 6, as molecules that block, inhibit, or neutralize the biological activity of TCCR. One example of an antagonist recited in the specification is an anti-TCCR antibody. Applicants submit that having the structure of the receptor TCCR provided in the specification, production of an anti-TCCR antibody is a routine exercise in this art. Further, the Examples adequately describe, with reasonable predictability, that blocking, inhibiting, neutralizing, or "knocking out" the biological activity of TCCR results in loss of Th_1 responses and in the differentiation of T cells into a Th_2 subtype (see Example 12 at pages 103-105).

The structure of antibodies and methods of making antibodies are well known. Such methods are described in the specification at pages 67-74. Several screening assays for antagonists are also described at pages 59-60 of the specification. In addition, a working example of an *in vitro* assay for detecting differentiation of cells into Th_1 or Th_2 cell type is provided at page 104, lines 1-11 and pages 105-106, bridging paragraph. This assay can be used to screen for antagonists that enhance differentiation into the Th_2 cell type and inhibit differentiation into the Th_1 subtype.

Another example of an antagonist described in the specification is an antisense molecule. Nucleic acid sequences encoding TCCR are provided in the specification, as well as the locations of specific domains of the TCCR polypeptide. Methods for preparing antisense molecules are described at page 65. The specification discloses a number of screening assays for antagonists at pages 59-60, and provides a working example of an assay at page 105. Thus, Applicants submit, on reading the specification and the Examples provided, possession of antagonist antisense molecules is readily demonstrated.

Given the structural and functional characterization of TCCR, the screening assays provided, including the T cell differentiation assay, and the known structure and methods of

making antibodies and antisense molecules, Applicants assert possession of the claimed TCCR antagonist is fully demonstrated. Removal of this rejection is requested.

35 U.S.C. 112, Enablement

Claims 1-5 and 11-13 were rejected under 35 U.S.C. 112, first paragraph, as not enabled by the specification. The Examiner contends that the specification does not provide specific guidance to make and use a diverse and representative number of antagonists. In addition, the Examiner contends that *in vivo* therapies for treatment of disease are unpredictable. Finally, the Examiner contends that treating a Th_1 mediated disease is also unpredictable. Applicants respectfully traverse this rejection.

As discussed above for Written Description, Applicants assert that the specification provides adequate guidance to permit one in this art to make and use TCCR antagonists without undue experimentation. Factors to be considered in an analysis of enablement include breadth of claims, nature of the invention, the state of the prior art, the level of ordinary skill, level of predictability in the art, the amount of direction provided by the inventor and the existence of working examples, and the quality of experimentation. MPEP § 2164.01(a) citing *In Re Wands*, 858 F2d 731, 737 (Fed. Cir. 1988).

As an initial matter, Applicants assert the specification, including the knockout mice example, define the activity of TCCR with sufficient predictability to enable one of skill in the art to make and use the claimed antagonists in a useful way. Several references teach the use of knockout mice to provide strong evidence of function of the knocked out gene and its encoded protein. See, for example, Huhtaniemi et al., 2002, *Mol. Cell Endocrin.*, 187(1-2):49; Stewart et al., 1992, *Nature*, 359(6390):76. In addition, no specific technical reason or evidence has been asserted by the Examiner to suggest that the knockout mouse described in the specification would be subject to the concerns raised by the Examiner and the Mak et al. reference.

Secondly, as discussed above, Applicants submit that the specification describes the structure and function of TCCR. In addition, several methods for screening antagonists of TCCR have been described, including a working example of an assay for differentiation of T cells to the Th_1 or Th_2 subtype.

As discussed above, one embodiment of an antagonist is an antibody to TCCR. The method of making antibodies as well as the structure of antibodies is well known to those of skill in the art and is described in the specification (pages 67 to 75). Thus, Applicants submit antagonist antibodies to TCCR can be made and used without undue experimentation.

Likewise, antisense molecules are described as antagonists of the invention. Nucleic acid sequences encoding TCCR, the locations of specific domains of the TCCR polypeptide, and methods for preparing antisense molecules have been described. Screening assays for antagonists are described at pages 59-60 and a working example of an assay is provided at page 105. Thus, using the information and guidance provided by the specification, antisense molecules that antagonize TCCR can be made and used without undue experimentation.

A considerable amount of experimentation is permissible if it is routine or if the specification provides a reasonable amount of guidance as to the direction experimentation should proceed. *In re Wands, supra.*

Applicants also assert that the specification provides sufficient guidance to use the described antagonists of TCCR to treat Th_1 mediated disease and to enhance T cell differentiation into the Th_2 subtype. With respect to the Examiner's contention that pharmaceutical therapies in absence of *in vivo* data are unpredictable, Applicants submit that *in vivo* data is not required to establish enablement. *In vitro* data is sufficient to establish enablement if it is reasonably correlated to the *in vivo* animal model. MPEP § 2164.02, citing *In Re Brana,* 51 F3d 1560 (Fed. Cir. 1975).

Applicants have described and provided a working example of an *in vitro* assay demonstrating differentiation of Th_1 and Th_2 cells that correlates with observed phenotypes in the knockout mouse model. Furthermore, T cells obtained from TCCR deficient KO animals were demonstrated to differentiate into cells lacking Th_1 mediated function, and to possess Th_2 mediated function. Thus, Applicants submit the claimed invention, for example, inducing T cell differentiation into Th_2 subtype and thereby reducing the functional effects of the Th_1 subtype, is enabled by the specification.

In addition, the use of antagonist antibodies and antisense molecules to block a biological function and thereby treat disease induced by that function is well-recognized. The Examiner has not provided any technical reason why the claimed antagonists, such as antibodies or

antisense molecules, might be inactivated or not reach the target area, or that a means to avoid these potential problems is not already known in the art.

Finally, the Examiner contends that methods of treating Th_1 diseases is complex and that applicants have not provided any working examples of using antagonists to treat Th_1 mediated disease. The Examiner suggests that *in vivo* data is required. Applicants submit that sufficient guidance to make and use the claimed invention has been provided, and that *in vivo* evidence is not required to meet the enablement standard. As discussed previously, *in vitro* data is sufficient to establish enablement if it is reasonably correlated to the *in vivo* animal model. MPEP § 2164.02 citing *In Re Brana,* 51 F3d 1560 (Fed. Cir. 1975). Applicants have described and provided a working example of an *in vitro* assay correlating removal of TCCR with differentiation of T cells into Th_2 subtype and loss of functional Th_1 subtype. This assay correlates with the observed phenotypes in the knockout mouse model. Accordingly, Applicants submit the claimed invention is fully enabled. Removal of the enablement rejection is requested.

SUMMARY

Applicants submit the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative to clarify any of the above remarks or to otherwise speed prosecution of this application.

Respectfully submitted,

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MARKED-UP VERSION TO SHOW CHANGES MADE

IN THE TITLE

Please amend the title as follows:

--[TYPE I CYTOKINE RECEPTOR TCCR] TCCR MEDIATED T-CELL DIFFERENTIATION--

IN THE SPECIFICATION

Please amend the specification as follows:

The paragraph beginning at page 18, line 14, has been amended as follows:

--Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al., Nucleic Acids Res.* 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from [http://]www[.]-ncbi.nlm.nih.gov or otherwise obtained from the National Institutes of Health, Bethesda, MD, USA 20892. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmark = yes, strand = all, expected occurrences = 1-, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph beginning at page 21, line 29, has been amended as follows:

--Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al., Nucleic Acids Res.* 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from [http://]www[.]-ncbi.nlm.nih.gov[.] or otherwise obtained from the National Institutes of Health, Bethesda, MD USA 20892. NCBI-BLAST2 uses several search parameters, wherein all of those search

parameters are set to default values including, for example, unmark = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--